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EXAMINER	
BETTON, TIMOTHY E	

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1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,273	VAISMAN, JAKOV	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-64,66,69-80 and 82-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-64, 66, 69-80, and 82-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Response filed on 29 October 2008 has been acknowledged and duly made of record.

The essence of applicants arguments are drawn to the rejection under 35 U.S.C. §112, second paragraph.

Applicant discloses:

Rejection under Claims 63-75 and 77-84 were rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear. This rejection is traversed.

As noted above, the claims have been amended to provide appropriate dependencies and to correct minor informalities. Applicant respectfully contends that the pending claims are not unclear or indefinite. Reconsideration and withdrawal of the rejection is proper and the same is requested.

Based on such disclosure by applicants, the Rejection under 35 U.S.C. §112, second paragraph is hereby withdrawn.

Further, applicants traverse the rejection under 35 U.S.C. §103(a).

Applicants claim that Crenshaw et al. does not teach or disclose a method of administering an antidepressant to a male via a combination of two independent routes for treating premature ejaculation in a male, as required by the pending claims. Moreover, Crenshaw does not teach or disclose administration of an antidepressant via a combination of mucosal administration and local administration to at least part of the male genitalia, as recited in the pending claims.

Applicants teach that Krushinski et al. does not teach or disclose that SRIs are to be administered via separate routes.

Applicants teach that Smith cannot remedy the deficiencies of the Crenshaw and/or Krushinski references. Smith teaches that a selected pharmacologically active agent is administered to an individual with a history of premature ejaculation. The active agent may be administered orally, parenterally, buccally, rectally, or locally by intracavernosal injection or by delivery to the urethra (Column 5, line 2-7). The pharmaceutical compositions according to Smith may also be administered by nasal aerosol or inhalation (Column 9, lines 36-38). Smith however, does not teach or disclose a method of administering an antidepressant to a patient **via a combination of two independent routes for treating premature ejaculation in a male.** Smith also does not teach or disclose a composition for the treatment of premature ejaculation comprising an antidepressant formulated for mucosal administration and for local administration to at least part of the male genitalia. **Smith merely teaches that drug delivery may be accomplished through any route effective to provide relief from premature ejaculation, including oral, parenteral, buccally, rectal, topical, transdermal, transurethral, and intracavernosal (column 3, lines 25-30).** Smith is completely silent as to the benefits of administering an antidepressant to a male via a combination of mucosal administration and local administration to at least a part of the male genitalia. Although Smith discloses a kit which may be used to assist an individual in administering a drug to treat premature ejaculation, Smith does not teach or disclose a kit comprising an antidepressant formulated for nasal administration and an antidepressant formulated for local administration to at least part of the male genitalia, as presently claimed in claim 85.

Applicants teach that Grass et al. does not teach or suggest the specific combination of routes of administration of the subject matter as presently claimed.

Applicants teach that the Bick, Hirai, Uda, and Rubsamen references either alone or in any combination fail to teach a method of treating premature ejaculation with the limitations as disclosed in the instant claims.

In view of the above, applicants arguments are considered but are not found persuasive.

The references *supra* are sufficient for what they separately and collectively teach essentially.

The central thrust of applicants' invention is directed to:

> As described in the present specification page 14, lines 1 3-1 6, all three routes of administration (oral, nasal, and a combination of topical and nasal) were found to produce a reduction in premature ejaculation as a whole. Surprisingly however, those subjects taking the antidepressants by both nasal administration and local administration to at least a part of the male genitalia noted particularly good results (Specification, page 15, lines 4-6).

Applicants' claims are all essentially dependent from claim 62 which discloses the limitation *comprising* which reasonably encompasses the teachings of all the references as cited in the current 103(a).

Applicants' claim 62 does not necessarily preclude or exclude administering in any of the other ways not disclosed in instant claim based on the term *comprising.*

Specifically, the disclosure of Smith et al. adequately supports and suggests obviousness over the current invention.

Obviousness to try is evident by the nature of the invention. The male genitalia by virtue of therapeutic application would reasonably begin via application locally (topically) especially in the case of sexual intercourse. The state of the art is replete with embodiments drawn to the initial application locally to the male genitalia in order to achieve a required therapeutic response (i.e., lubricants, spermicides, analgesics, etc.).

Smith et al. sufficiently makes the claimed invention obvious by directly teaching the combination of SRI and a monoamine oxidase inhibitor (column 2, lines 21 and 22).

Accordingly, Grass et al. fully teach and encompass the limitation drawn to the claimed specific combination of routes of administration by the teachings already made of record, (please see Office Action, (pp.7-10).

Grass et al. essentially teach the motivation to combine the references as disclosed in obviousness over the claimed invention. Grass et al. teach conventional modes of administration and combinations thereof based on the physiological make-up of any particular part or compartment of the body. Via the well-known art of pharmacokinetics, optimal combinations with regard to therapeutic administration are well-established in the art. Dual therapy as may be attributed to the claimed invention is a well-known protocol in the art of pharmacokinetics.

The Bick, Hirai, Uda, and Rubsamen references have been reconsidered and are hereby withdrawn.

Thus, for the reasons already made of record, the current rejection under 35 U.S.C. §103(a) is maintained.

Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 62, 64, 69-71, 76, 82, 83 and 85 have been amended to correct minor informalities and/or to more particularly point out and distinctly claim certain subject matter. Claims 63, 64, 66, 69-75, 77-80, and 82-84 have been amended to provide appropriate dependency and remove dependencies on cancelled claims. No new matter has been added.

Claims 65, 67, 68, and 81 have been cancelled without prejudice or disclaimer. Now pending in the application are claims 62-64, 66, 69-80, and 82-85.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 62-64, 66, 69-80, and 82-85 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Crenshaw et al. (U.S. Patent No. 5,151,448) and Choi et al. (USPN 5,587,167) in view of Smith et al. (USPN 5,922,341) and El-Rashidy (USPN 5,256,652).

Crenshaw et al. teach fluoxetine [which] is a known antidepressant and is commercially available under the trade designation Prozac.RTM. as fluoxetine hydrochloride. This compound can be represented by the formula as disclosed and is also known by its chemical name as **(.+-.)-N-methyl-3-phenyl-3-[(.lambda., .lambda.,.lambda.-trifluoro-p-tolyl) -oxy]propylamine hydrochloride.** The molecular weight of fluoxetine hydrochloride is 345.79. It is a white to off-white crystalline solid and exhibits a solubility in water of about 14 milligrams per milliliter (column 1, lines 64-68; column 2, lines 10-15 and 20-68)

It has now been found that premature ejaculation in a male human patient suffering from such an affliction can be effectively ameliorated and treated by the administration to the patient of an effective dose of fluoxetine either in its free base form or its acid addition salt form. Fluoxetine is an amine, and, as is well known, amines readily form acid addition salts with inorganic acids as well as organic acids (column 2, lines 20-27).

The term "fluoxetine," as used herein and in the appended claims, means the free base form as well as an acid addition salt form of **(.+-.)-N-methyl-3-phenyl-3-[(.alpha.,.alpha.,.alpha.-trifluoro-p-tolyl)-ox y]propylamine.** (column 2, lines 28-30).

For the treatment contemplated by the present invention, the preferred route of administration is oral administration; however, **other routes of administration, e.g., parenteral, by suppositories, buccal dosage forms, skin patch, and the like**, can also be utilized. The active ingredient in the individual dosage forms can be **combined with the conventional pharmaceutical excipients and formed into tablets, capsules, and the like**. Tablets may be scored for divided dosage administration. Alternatively, the active ingredient

may be dissolved in a suitable liquid vehicle such as water, fruit juice, or the like. For chronic administration of the active ingredient oral dosage forms are preferred (column 2, lines 64-68; column 3, lines 1-8).

The dosage formulation drawn to suppositories is considered mucosal dosage forms in accordance with buccal dosage forms. The skin patch adequately teaches topical administration and "and the like" further supports and suggests variable forms of topical administration.

Crenshaw et al. teach the antidepressant fluoxetine is administered in an amount of between 5 milligrams to about 80 milligrams per day (column 1, lines 55 and 56).

Crenshaw et al. does not teach embodiments drawn specifically to serotonin, which is well-known intrinsic component inhibited by serotonin reuptake inhibitors such as fluoxetine.

Crenshaw et al. does not teach topical or local administration to at least a part of the male genitalia.

Choi et al. teach [that] [t]he present invention relates to an ointment composition for prophylaxis and treatment of premature ejaculation in a male patient and more particularly to a composition for applying to the glans penis […] (abstract only). This disclosure clearly encompasses the limitation of local administration (abstract only).

Choi et al. does not teach mucosal administration.

However, Smith et al. teach [that] [t]he pharmaceutical compositions of the invention may also be administered by nasal aerosol or inhalation. […](col. 11, l/s 27-35).

Smith et al. teach a kit [which] is provided to assist an individual in administering a drug to treat premature ejaculation. Generally, the kit will include the following components: a pharmaceutical formulation comprising an active agent as provided herein; a device for effecting delivery of the pharmaceutical formulation; a container housing the pharmaceutical formulation during storage and prior to use; and instructions for carrying out drug administration in a manner effective to delay the onset of ejaculation (column 3, lines 45 and 46) (column 12, lines 54 and 55).

Smith et al. does not teach hydroxypropyl-β-cyclodextrin (HPBCD).

However, El-Rashidy teaches [a] number of trials have been conducted under physician supervision in volunteers diagnosed with premature ejaculation and who have not been able to maintain an erection for coitus. These patients were young, healthy subjects with normal vascular integrity and were undergoing treatment with intracavernosal injections of 30 mg doses of papaverine as part of a therapeutic regimen. These injections were substituted with a topical hydrogel formulation (Preparation 6 in Table II; 50 mg dose of papaverine). The patients were asked for a subjective evaluation of efficacy based on the quality of their erection (rigidity) and the duration of action. The patients were instructed to apply the topical preparation in the following manner.

In Example 7 (Trials in Patients), the embodiment is drawn principally to the treatment of premature ejaculation. Further, El-Rashidy teaches the topical application directly to parts of the male genitalia (column 3, lines 35-53).

Further in referenced claim 1 (column 14, lines 28-29), HPBCD is taught disclosing the same exact ranges as disclosed in instant claim 83.

Thus, it would have been *prima facie* obvious to the one of skill at the time of invention to recognize a reasonable expectation of success via the incorporating and combining together of the methods and teachings of Crenshaw et al., Choi et al., Smith et al., and El Rashidy.

The scope and contents of the prior art fully address and encompass the limitations disclosed in the current invention.

Crenshaw et al. teach fluoxetine for the treatment of premature ejaculation. Crenshaw et al. teach a dosage that fully supports and suggests obviousness over the limitation in the claimed invention. Crenshaw et al. does not teach the limitations drawn to a combination of mucosal and local administration. Choi et al. teach that a formulation may be administered locally (topically) to a part of the male genitalia for premature ejaculation. Smith et al. teach that a formulation containing an antidepressant such as fluoxetine may be administered nasally (mucosally). El-Rashidy also teach the disorder premature ejaculation by which HPBCD may be administered in a ratio that is the same exact ratio by which HPBCD is disclosed in the claimed formulation of the current invention.

The differences between the prior art and the claims at issue are that the references as cited have overlap and may not teach each and every element as disclosed in current invention separately. However, the references taken together fully address each and every limitation according to the claimed invention. Each reference addresses the central thrust of the current invention by teaching a formulation for premature ejaculation that is administered in

combination therapy mucosally and locally. The enhancer agent as taught by El-Rashidy is drawn to a formulation that is reasonably intended to treat premature ejaculation.

Objective evidence present in the application to indicate obviousness is that it would be readily obvious to apply a formulation for this specific indication/disorder, topically. It is art-known that in order to maximize therapeutic efficacy, more than one mode of administration would be necessary in order to achieve optimal therapeutic efficacy as an added measure. It is not uncommon for a sprained ankle to be treated with an analgesic balm while concomitantly being treated with an NSAID. Thus, the same motivation would be readily obvious to the one of ordinary skill in the pertinent art as described in this current invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access

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/Shengjun Wang/

Primary Examiner, Art Unit 1617

TEB